REMARKS

I. The claims

Claims 1-36 are pending. Claims 1-16 are presently withdrawn as a result of being deemed to be directed to a non-elected inventions and claims 21, 23, 26, 28, 31 and 33-35 are presently withdrawn as being drawn to non-elected species.

Elected claims 17-20, 22, 24, 25, 27, 29, 30, 32 and 36 were examined on the merits and were rejected in the Office Action mailed February 13, 2006, but were found to be free of the prior art. (Office Action, ¶7.)

Claims 18, 20 and 29 have been amended herein in connection with Applicant's response to the claim rejection under 35 U.S.C. §101, and to more clearly point out what Applicant regards as the claimed invention.

No new matter has been added by any of the amendments made herein.

II. Claim rejections under 35 U.S.C. §101

Claims 18-20, 22, 29, 30 and 32 were rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter since the scope of the claims allegedly encompasses a human being. (Office Action, ¶¶3 and 4.)

The present rejection is overcome for the following reasons.

Claims 18 and 29 have been amended to recite that the claimed cell is "not integrated with a human being." This negative language parallels the language of the Examiner on page 3, lines 8-9 of the Office Action. Claim 20 has been amended to recite that the claimed multi-cellular organism is "non-human."

Applicant wishes to point out that, consistent with USPTO policy, the scope of the claims covers, *inter alia*, human cells but does not encompass a human being.

In view of the above, withdrawal of the present rejection under 35 U.S.C. §101 is hereby requested.

III. Claim rejections under 35 U.S.C. §112 – enablement requirement

Claims 17-20, 22, 24, 25, 27, 29, 30, 32 and 36 are rejected for allegedly failing to comply with the enablement requirement under 35 U.S.C. §112, first paragraph. (Office Action, ¶4.) Under the heading "Breadth of the Claims" on page 4 of the Office Action, the Examiner has asserted that the aspects of the claimed invention considered broad are: "(i.) the cell to be genetically modified and (ii) the polynucleic acid molecule having at least one region of predetermined sequence" and that these aspects are not enabled for their full scope.

The present rejections of the claims are overcome for the following reasons, which are directed to each part of the Examiner's asserted "Wand's Factors" analysis.

(A.) Under the heading "The Nature of the Invention" on page 5 of the Office Action, the Examiner asserts that "the invention is within the broad genera of gene targeting and gene targeting does not generally enable Applicant's invention due to problems with the complexity and unpredictability of such methods," citing Kolb et al., Trends in Biotechnology, 2005, 23: 399-406 ("Kolb"). The conclusion drawn from the cited passage by the Examiner is that "the Artisan would not reasonably predict that the [sic] any cell genetically modified as claimed could be used to regulate gene expression.

A careful reading of the cited excerpt of Kolb and the Kolb reference as a whole reveals that the Examiner's reliance on Kolb for this aspect of the rejection is improper.

First, the cited Kolb reference is specifically directed to novel and developing technologies within the field of gene targeting, as shown by the following passage:

> "In an accompanying article in this issue of Trends in Biotechnology, we outline methods for achieving targeted integration and gene repair by using the innate DNA recognition abilities of recombinases and transposases. This review will focus on strategies to engineer enzymes with novel DNA targeting abilities."
>
> [Kolb et al. Trends in Biotechnology, 2005, 23: page 399 col. 2, line 16; emphasis added.]

It is abundantly apparent that the limitations described in the passage of Kolb relied upon by the Examiner apply to new enzyme engineering strategies and not to the random integration or homologous recombination methods that are commonplace within the art. Indeed, the biological sciences literature and even the lay press have been replete for some time with reports of transgenic knock-in and knock-out animals, including mammals such as mice and pigs. Thus, the Examiner's reliance on the Kolb reference is improper.

Second, the cited passage is specifically directed to "[g]ene repair and targeted integration... for gene therapy and animal transgenesis." The presently claimed invention is not directed to "gene repair" and "gene therapy" which implicitly require high efficiencies in many cells to correct some deficiency in a preexisting organism. With respect to "animal transgenesis," if this term means creating a transgenic animal, the pending claims do not require it. However, an animal that is transgenic to embody the presently invention is within the scope of the claims. For example, U.S. Patent No. 6,242,667 issued June 5, 2001, which is of record in and incorporated by reference in the present application, teaches the production of transgenic animals having tetracycline-regulated transcriptional regulatory systems. (See originally-filed specification, page 17, l. 15-18.)

(B.) Under the heading "The State of the Prior Art and the Level of Predictability in the Art / Amount of Experimentation Necessary" on page 6, l. 12-14, of the Office Action, the Examiner asserts states that "the issue is whether or not such a claimed regulation of gene expression could have been practiced by a person skilled in the art without due experimentation at the time the invention was made." The Examiner's specific contentions in this regard are responded to individually in each case, as follows.

(B1.) The Examiner has asserted that: "[i]n order for this methodology to work, the above-mentioned series of DNA sequences must be integrate into the cell genome. This can take place by two main processes: transfection or homologous recombination." (Office Action, page 6, l. 20-22.)

Applicant wishes to point out that "transfection" refers to the introduction of DNA into a cell, not to the type of integration process itself. However, Applicant

believes that by "transfection" the Examiner intended to mean random integration. (Constructs for random integration or homologous integration may each be transfected into a cell.) Examples of the sort of integration that may be used for the present invention is described in the art of record, for example, in U.S. Patent Nos. 6,242,667 and 5,723,765, each of which is also incorporated by reference in the subject application.

(B2.) The Examiner has also asserted that: "[i]n case of [sic] transfection is used, how would one of skill in the art know to transfect the foreign DNA such that the encoded product is efficiently expressed (i.e., avoiding the chromosomal positional effects that adversely affect expression), without disturbing expression of essential genes? Introduction of transgene into cells is inefficient and can be accompanied by potentially mutagenic random integration into the genome; alternately, random insertion can lead to inefficient expression," citing Coates et al., Trends in Biotechnology, 2005, 23: 407-419 ("Coates"). (Office Action, page 7, l. 4-14.)

First, high efficiency is not required for enablement. Indeed, those knowledgeable in the art appreciate that one or more available selection schemes are routinely used in the art in the production of genetically modified cells and organisms. Second, the alleged problems and overcoming them are part of the routine yet complex experimentation that is performed in laboratories worldwide in the production of genetically modified cells and organisms. Further, it is appreciated in the art that expression cassettes and systems are widely available, in many case commercially available, which allow expression in a wide variety of cell types. Indeed, the art made of record in the present application, including numerous issued patents, indicates that the genetic modification of cells and organisms is a standard practice within the art. Again, U.S. Patent No. 6,242,667 issued June 5, 2001, which is of record in and incorporated by reference in the present application, teaches the production of transgenic animals having tetracycline-regulated transcriptional regulatory systems. U.S. Patent No. 5,723,765 issued March 3, 1998, which is of record and incorporated by reference in the present application, teaches the production transgenic plants that embody a tetracycline-responsive recombinase expression and DNA excision system. (See originally-filed specification, page 17, l. 15-18.) Further, Aoyama et al. (1997), which is of record in the present application, teaches the production of transgenic plants having a glucocorticoid-

mediated transcriptional induction system based on heterologous transcriptional regulators. In further response, the Examiner is also respectfully directed to the discussion of the cited prior art below.

With specific respect to Coates, Applicant first wishes to point out that the focus of the article is "on how natural DNA-modifying enzymes could be modified so that they mediate site-directed integration of DNA." While Coates' stated focus articulates an laudable goal, it also illustrates the author's bias and rationale for stressing alleged shortcomings in presently used methods. Second, a full reading of Coates shows that the reference is actually definitively supportive of the enablement of gene integration for the present invention. In this regard the Examiner is directed to Table 2 on page 416 of Coates which describes six different gene integration systems, and their frequency of use in many laboratories for four of the six and use in several laboratories by the remaining two. Further, in describing Table 2, the Conclusions section of Coates (on page 416, left-hand column) states "[s]table transgene insertions into host genomes can be catalyzed by several available viral, transposon and recombinase systems (Table 2)." (Emphasis added.) Table 3 of Coates (also on page 416) specifically describes integration frequencies for three gene transfer systems, which are all workable, and refers to the ability in some of the cited cases to select cells arising from desired integration events. (Emphasis added.) Thus, despite the cited passage of Coates that "integration at random sites often places the transgene into an environment that is not supportive of its expression," well established selection schemes known in the art can (and are) used to obtain genetically modified cells expressing to a desired extent.

(B.3) With respect to alleged problems arising from random insertion, the Examiner has cited Wurtele et al., Gene Therapy, 2003, 10: 1791-1799 ("Wurtele"). (Office Action, page 7, l. 15 – page 8, l. 10.) Applicant respectfully submits that the Examiner's cited passages are taken out of context and do not support Wurtele's affirmative teachings that:

> "Foreign DNA integration is one of the most widely exploited cellular processes in molecular biology. Its technical use permits us to alter a cellular genome by incorporating a fragment of foreign DNA into the chromosomal DNA."

[Wurtele, page 1791, Abstract, l. 1-4; emphasis added.]

"The development of methods to manipulate and modify the genome is one key achievement of molecular biology. Foreign DNA integration is one of the most widely used techniques, allowing us to modify a cell's genetic content."

[Wurtele, page 1791, Introduction, left-hand col., l. 1-5; emphasis added.]

Applicant acknowledges that Wurtele discusses problems that may be caused by illegitimate DNA integration. However, the selections and analyses that are routinely performed have allowed and continue to allow those skilled in the art to obtain foreign DNA integration having desired characteristics on a routine basis. Moreover, Applicant wishes to point out that illegitimate integration is not necessarily deleterious to the presently claimed invention – indeed, nothing in the present claims limits the genetically modified cells or organisms to those having only the desired integration, nor does anything in the present claims limit the genetically modified cells or organisms to those having wild-type characteristics.

(B4.) With respect to homologous recombination, the Examiner has cited Vasquez et al. (Proc Nat'l Acad Sci USA, 2001, 98, 8403-8410; "Vasquez") and asserts that "[b]y contrast, homologous recombination provides a precise mechanism for targeting defined modifications to genome in living cells. However at the time the invention was made, and even in the present, the technology was presented with difficulties and the outcome was unpredictable." (Office Action, page 8, l. 11–26)

First, Applicant must point out that one excerpt of the Examiner's cited passage of Vasquez is particularly instructive: "[t]hus, gene targeting is now a standard tool, however, does not mean that gene targeting is easy or that success is assured. Indeed, its application requires a certain persistence and effort that is not necessary, for example, in *Saccaromyces cerevisiae*." (Office Action, page 8, l. 19-21; emphasis added.)

Enablement does not require that the subject task is "easy" – it is enough for enablement that gene targeting is a standard tool that requires persistence, as presumably acknowledged by the Examiner by way of the cited passage above. With this persistence, there is a reasonable expectation of success. Indeed, persistence and complex

experimentation are hallmarks of biotechnology research and development activities. As explained in the MPEP:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.
>
> [MPEP §2164.01, Undue Experimentation; emphasis added.]

(B.5) With respect to homologous recombination in plants, the Examiner has cited several passages from Iida et al., Plant Molecular Biology (2005) 59: 205-219 ("Iida") to assert that gene targeting in higher plants is not enabled. (Office Action, page 8, l. 27 – page 9, l. 7.) Each of the specific passages cited by the Examiner is addressed below.

The Examiner cited Iida: "[i]n higher plants, however, the overwhelming occurrence of the random integration of transgenes by non-homologous end-joining is the main obstacle to develop efficient gene targeting." (Office Action, page 8, l. 28-30; emphasis added.)

Applicant wishes to point out that efficiency is not required for enablement. Moreover, the presently rejected claims do not require a minimum efficiency. What is required for enablement is that a skilled worker in the art engaging in experimentation typical of the art can practice the invention. [See above-cited passage of MPEP §2164.01, Undue Experimentation.] Complex experimentation is typical in the biotechnological arts and is typical for creating genetically modified cells and organisms. In addition, it is well recognized in the art and in several of the references cited by the Examiner that the genetic modification of cells and organisms is a routine practice in the art, as described below.

The Examiner has also cited Iida: "[i]n addition to random integration mediated by non-homologous end-joining, the occurrence of aberrant recombination events associated with homologous gene targeting, called one-side invasion and ectopic targeting, has also been reported." (Office Action, page 8, l. 31-33.)

Applicants wish to point out the following. First, nothing in the cited passage indicates that this is a common problem that prevents skilled workers from obtaining the desired genetically modified cells or organisms, only that it has been "reported." Indeed, the fact that the alleged defect can be detected at all indicates that is can be selected or screened against using routine techniques. Second, aberrant targeting is not necessarily a problem with respect to the presently claimed invention. If a homologous recombination technique is used to obtain a genetically modified cell according to the presently claimed invention, what is important is that the desired homologous targeting event occurs, irrespective of what other aberrant events may occur. Moreover, as discussed above, random insertion may also be used.

The Examiner has also cited Iida: "[t]here has been a single report describing the successful and reproducible targeting of the endogenous Waxy gene without concomitant occurrence of an ectopic event... [h]owever, no article of another natural endogenous gene in rice has been published in the past 2 years since the first report, indicating that the progress of gene targeting in rice is apparently not so fast and we still need to accumulate more knowledge and know how to improve the procedure." (Office Action, page 9, l. 1-7.; emphasis added)

Applicant wishes to point out the following reasons why the asserted support for the rejection is improper.

First, Iida itself contradicts the Examiner's assertion. The cited passage does not take into account the work of Iida – which shows that the prior Waxy gene work of Terada et al. (2002) is generally applicable to other genes. The homologous recombination dependent targeting of the rice Waxy locus is described on page 213 of Iida. As described on page 213, left-hand column, 4th line from bottom through right-hand column, line 9, homologous recombination using strong positive-negative selection in rice resulted in the precise targeting of the Waxy locus without ectopic events.

Importantly, the authors confirm that the technique used to precisely target the Waxy locus is "[b]ecause, this strategy is independent of gene-specific selection, in principle, applicable to any other gene" and that "[p]reliminary results indicated that we were indeed able to repeatedly obtain transplants plants having the Adh2 gene disrupted with frequency comparable to the published targeting frequency of the Waxy gene." (See Iida, page 213, right-hand column, l. 9-27; emphasis added in quoted passages.) Thus, what Iida has shown is that the earlier method of Terada et al. (2002) is generally enabling for genes. Therefore, the presently claimed invention was enabled at the time of filing.

Second, again, if a homologous recombination technique is used to obtain a genetically modified cell according to the presently claimed invention, what is important is that the desired homologous targeting event occurs, irrespective of what other ectopic events may occur. The presently rejected claims do not require that the genetically modified cells do not contain ectopic insertions.

(B.6) The Examiner has also asserted that "another unpredictable aspect of the invention is the silencing of the transcript encoding for a transcriptional repressor protein that controls the expression of the site-specific recombinase. (Office Action, page 9, l. 8-10.) The Examiner has first specifically asserted that is "not always true" that"the absence of the repressor protein would allow for the expression of the site-specific recombinase." (Office Action, page 9, l. 10-12.) The Examiner then asserts that since "transcription is carried out by assemblies of transcription factors, and many of them are redundant in the cell," "how would one skilled in the art know that inhibition of any repressor would result in efficient expression of the desired site-specific recombinase without undue experimentation." (Office Action, page 12, l. 20-26; emphasis added.)

This aspect of the rejection is overcome for the following reasons.

First, Applicant wishes to point out that is not necessary for all embodiments to always work, i.e., "always be true," to have enablement. As explained in the MPEP:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is

normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

[MPEP §2164.08(b) Inoperative Subject Matter; emphasis added]

Second, the Examiner's statement is not founded in that the present claims are not directed to "any repressor" but instead recite "...a cell comprising a series of DNA sequences that includes an excisable sequence element that is bounded on either side by specific excision sequences, a repressible promoter operably linked to a gene encoding a site specific recombinase capable of recognizing the specific excision sequences, and a gene operably encoding a repressor protein specific for the repressible promoter..." (Originally filed specification, claim 17; emphasis added; similar language also recited by independent claims 18 and 29.). Thus, the claims explicitly recite that the repressor is specific to the repressible promoter that, in turn, is operably linked to the gene encoding a site specific recombinase.

Third, the claims do not require "efficient" expression to be achieved; the language of the claims implicitly conveys that an at-least-adequate expression of the recombinase to effect the recited excision is required. However, Applicant nevertheless wishes to point out that suitably robust expression systems for various biological systems are not only known in the art and available "off-the-shelf," but are also described within the originally-filed specification. For example, see again, U.S. Patent No. 6,242,667 issued June 5, 2001, which is of record in and incorporated by reference in the present application, teaches the production of transgenic animals having tetracycline-regulated transcriptional regulatory systems. U.S. Patent No. 5,723,765 issued March 3, 1998, which is of record in and incorporated by reference in the present application, teaches the production transgenic plants that embody a tetracycline-responsive recombinase expression and DNA excision system. (See originally-filed specification, page 17, l. 15-18.) Further, Aoyama et al. (1997), which is of record in the present application, teaches the production of transgenic plants having a glucocorticoid-mediated transcriptional induction system based on heterologous transcriptional regulators.

Three, in response to the question posed in the Examiner's rejection, it is not seen how determining whether eliminating the function of one or more particular transcription factors that operate together affects transcription can be undue experimentation or even required to practice the invention since such experiments are of a classical and routine nature in the art and since the invention may use recombinant DNA constructs formed of selected genetic elements (selected promoters, recombinase encoding and excision sequences, etc.) by recombinant techniques. Thus, the Examiner's comment is purely hypothetical and does not properly reflect on enablement. Still, *in arguendo,* if it were somehow necessary (even for the sake of curiosity) to eliminate the function of two or more redundant transcription factors to induce expression of the recombinase, this can be readily determined, for example using commercially available anti-sense or RNA silencing reagents, and there is nothing precluding a skilled worker from applying the present invention to the two or more factors. Indeed, such a strategy would be obvious to a skilled worker having the benefit of the present specification. Applicant also wishes to point out that various articles made of record in the present application show that RNA/gene silencing of selected genes was readily available for the above-described purpose. See, e.g., Wesley et al. (2001) Construct design for efficient, effective and high-throughput gene silencing in plants, The Plant J. 27(6), 581-590; Paddison et al. (2002) Stable suppression of gene expression by RNAi in mammalian cells, Proc. Nat'l Ac. Sci. USA 99(3) 1443-118; and Piccin et al. (2001) Efficient and heritable functional knock-out of an adult phenotype in Drosophila using a GAL4-driven hairpin RNA incorporating a heterologous spacer, Nuc. Acid Res. 29(12) e55 page 1-5.

In view of the above, these particular bases of rejection are overcome.

(C.) Responses to aspects of rejection for alleged non-enablement of RNA silencing

Further under the heading "The State of the Prior Art and the Level of Predictability in the Art / Amount of Experimentation Necessary" (beginning on page 6, l. 12-14), of the Office Action, the Examiner has asserted several alleged bases for non-enablement that directed to the RNA silencing aspect of the presently claimed invention. (Office Action, page 10, line 6 – page 12, l. 25.) The examiner has asserted that "the use

of short interfering nucleic acid to target genes is well known to be an unpredictable art." (Office Action, page 10, l. 8-9)

First, Applicant wishes to point out again that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (MPEP §2164.01, Undue Experimentation). The selection of RNA silencing inducing polynucleic acid molecules using algorithms and/or trial-and-error testing, based on the sequence of a desired target, has been a long-standing standard and routine experimental procedure within the art of molecular biology. Indeed, the Examiner should appreciate that a supporting industry of RNAi reagent suppliers has been in place for a number of years.

Second, Applicant submits that there was sufficient predictability in the art to fully enable the presently claimed invention at the time of filing. This is shown, for example, by the following documents that are of record in the application:

1. Wesley et al. (2001) Construct design for efficient, effective and high-throughput gene silencing in plants, The Plant J. 27(6), 581-590;
2. Paddison et al. (2002) Stable suppression of gene expression by RNAi in mammalian cells, Proc. Nat'l Ac. Sci. USA 99(3) 1443-118;
3. Piccin et al. (2001) Efficient and heritable functional knock-out of an adult phenotype in Drosophila using a GAL4-driven hairpin RNA incorporating a heterologous spacer, Nuc. Acid Res. 29(12) e55 page 1-5.

Third, each of the Examiner's assertions based on the cited passage of the prior art is addressed specifically in the subsections below.

(C1.) Examiner's assertions based on Sledz et al. (2005)

First, Applicant wishes to point out that the affirmative teachings of the cited Stedz reference in support of enablement of the present invention must be considered. For example, on page 787, the Abstract of Sledz teaches:

> "Over the past 5-years, an intensive effort has facilitated the movement of RNAi from a relatively obscure biological phenomenon to a valuable tool used to silence gene expression and perform large-scale functional genomic screens. In fact,

recent studies in this journal and others have demonstrated the success using RNAi to address the role of oncogenic expression in leukemia cell lines and to validate the therapeutic potential of RNAi for treating these blood disorders."

Below the passage of Sledz cited by the Examiner on page 10 of the Office Action, the Examiner has asserted that "the problems of short interfering nucleic acids based therapies are well known in the art, particularly with regard to RNAi resistance, with regard to the inability to deliver and effective concentration of a nucleic acid to a target cell and with regard to unpredicted nonspecific effects. (Office Action, page 10, l. 24-28.) These bases for rejection are inapplicable to the present claims because: (1.) Applicants are not claiming a therapy; (2.) because a therapy of a *non*-genetically-engineered organism is not what is claimed, the delivery concerns specific to a therapy are not an issue; and (3) non-specific effects do not necessarily pose any problem with the claimed invention so long as the desired target is silenced.

(C2.) Examiner's first assertions based on Woessmann et. al. (2003)

The first passage of Woessmann et al. (cited by the Examiner on page 11, lines 3-10 of the Office Action) specifically alleges "extreme sequence specificity of RNAi" and describes mutations that can keep a tumor resistant to RNAi. The present claims do not relate to treatment of a tumor. Problems in the context of treating a tumor with RNAi, such as may relate to genetic mutation of tumor cells, are not applicable to the present claims.

The second passage of Woessmann et al. (cited by the Examiner on page 11, lines 11-13 of the Office Action) describes potential (note use of word "could") antagonism of RNAi by the RNA editing process. Applicant wishes to point out that while this potentially could be a problem in any cell having RNAi editing machinery, it is not a particular problem at all for the presently claimed invention since ,in contrast to targeting an endogenous, naturally occurring gene, the cells of the presently claimed invention are genetically engineered to comprise specific DNA sequences – thus any hypothetical concerns, if actually realized, can be addressed by modifying a gene to eliminate or change the RNA-editing. For example, it is well known to construct a mini-gene of a

protein coding gene that does not contain any introns and to use such a mini-gene for expression in a cell rather than using the naturally occurring intronic form of the gene.

(C3.) Examiner's assertions based on Opalinska et al. (2002)

The Examiner has cited the following passages of Opalinska et al. "with respect to specific delivery" although the Examiner appears to be insinuating further assertions from the passages. (Office Action, page 11, l. 14-34.)

(i.) "A newly developing approach for targeting mRNA is called post-transcriptional gene silencing, or RNA interference (RNAi)... The universality of this approach...an the types of gene that can be modified using this strategy in mammalian cells, remain unknown at this time."

(ii.) "[i]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms if reliability [120, 121]. [See page 11 of Office Action for intervening passage] Attempts to accurately predict the in vivo structure of RNA have been fraught with difficulty. Accordingly mRNA targeting is a random process."

(iii.) "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, olgonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytisis. After internalization confocal and electron microscopy studies have indicted that the bulk of them enter the endosome-lysosome compartment, in which most of the material becomes trapped or degraded."

First, Applicant wishes to point out that the Opalinska et al. reference is a review of nucleic acid based therapeutics (see title and whole document) in general and is not specific to RNA silencing approaches. Applicant submits that the applicability of certain cited statements to RNA silencing specifically in the article and the authoritativeness of the statements with respect to RNA silencing is questionable and therefore should not be relied upon.

Passage (i.) is irrelevant to the enablement of the presently claimed invention because it does not relate to "delivery" for which the Examiner has specifically relied on the reference for and because whether any technique is "universal" for mammalian cells or cells of any genera can never be known with any certainty and enablement requirement does not require it.

Passage (ii.) asserts that ""[i]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms if reliability.[120, 121]" (See passage above.) Applicant wishes to point out that this assertion is generally made and there is no indication that among the various types of targeting described in Opalinska et al. that the statement refers to RNA silencing specifically. Further to this, Applicant wishes to point out the references (nos. 120 and 121) cited by Opalinska et al. for the statement, were not included in the passage as printed in Office Action. Applicant respectfully requests the Examiner is directed to page 514 of Opalinska et al. where citations for 120 and 121 are listed. Citation 120 is Gerwitz et al., Facilitating oligonucleotide delivery: helping antisense deliver on its promise (Proc. Nat'l Ac. Sci USA 93, 15481-15484 dated 1996. A traditional antisense article dated 1996 is not proper support for assertions about time-of-filing RNA silencing molecules methods. Citation 121 is Lebedeva et al. Antisense olgonuicleotides: promise and reality, Annu. Rev. Pharmacol. Toxicol. 41, 403-419 dated 2001. Accordingly, it is not seen how an authoritative statement about RNA silencing molecules can be made based on two articles relating to conventional anti-sense oligonucleotides, especially when one is dated to 1996.

Passage (ii.) also poses a conclusion that is illogical; specifically "[a]ttempts to accurately predict the in vivo structure of RNA have been fraught with difficulty. Accordingly mRNA targeting is a random process" is illogical and not correct. The conclusion that mRNA targeting is a random process cannot be drawn from the assertion that predicting RNA in vivo structure is difficult. As described above, the standard of enablement is not whether a task is difficult. Furthermore, the selection and testing of nucleic acid molecules for their ability to silence a target by RNA silencing may but does not necessarily have to involve prediction of a target RNA's in vivo secondary structure.

Still further, "mRNA targeting is a random process" appears to equate two opposites, random and targeted.

Passage (iii) relates to delivery of nucleic acids into cells. The statement is made broadly without recognizing differences between delivery of DNA ologonucleotides and small silencing RNA molecules that are recognized in the art. Moreover, reliance on this passage does not take into account that the originally-filed specification teaches that cells according to the invention can be genetically modified so that RNA silencing molecules, such as short hairpin RNAs as known in the art are express within the cell itself. (See, e.g., originally-filed specification, page 39, l. 22-25.)

(C4.) Examiner's second assertions based on Woessmann et al. (2003)

The Examiner has also cited Woessmann for the assertion that "unpredicted non-specific effects" of RNAi render the presently claimed invention lacking for enablement. (Office Action, page 11, l. 36 – page 12, l. 12.)

The selection below from the passage cited by the Examiner on page 12, l. 10-12, is particularly instructive.

> "Whether this finding may indeed seriously hamper the possibilities to develop gene-specific therapeutics on the basis of siRNA remains to be seen. To date, the prediction of the most effective but also specific siRNA for a particular target is not an easy task." (Emphasis added.)

With respect to the second cited passages of Woessmann et al., Applicants wish to point out the following. First, the cited passages specifically relate sto gene specific therapeutics. Applicant is not claiming siRNA based gene therapeutics – it is not relevant to the present claims whether there are nonspecific effects so long as silencing of the desired target occurs. Second, the cited passage is hardly conclusive (see passage above, "[w]hether this...may...hamper...remains to be seen"), and therefore reliance on the passage against the presently claimed invention is not proper. Third, the Examiner is again reminded that the proper standard for experimentation with respect to enable is not whether a task is "easy" but is instead whether "the art typically engages in such experimentation." (MPEP §2164.01, Undue Experimentation.)

(D.) Under the heading "The Amount of Direction or Guidance / The Existence of Working Examples" on page 12 of the Office Action, the Examiner asserts that "[t]he specification does not provide the guidance or working examples required to overcome the art-recognized unpredictability of using gene targeting applications in any cell or organism. The field of gene targeting does not provide that guidance, such that the skilled artisan would be able to practice the claims invention." (Emphasis added.)

The Examiner has also listed conclusions in connection with the asserted case of non-enablement under the heading "Conclusion" on page 13 of the Office Action). Each of the alleged conclusions in connection with the Examiner's asserted case of non-enablement is addressed in the discussion hereinabove.

Applicant has addressed each and every part of the Examiner's asserted Wand's analysis and conclusions in connection therewith by showing that the cited references were improperly relied upon by the Examiner and/or by showing enablement of the specific aspects of the invention with reference to the documents of record.

In view of the response set forth hereinabove, Applicant respectfully requests withdrawal of the claim rejections under 35 U.S.C. §112, paragraph 1 – enablement requirement.

IV. Conclusion

Claims 1-36 are pending. Claims 1-16 are presently withdrawn as a result of being deemed to be directed to a non-elected inventions and claims 21, 23, 26, 28, 31 and 33-35 are presently withdrawn as being drawn to non-elected species. .

Pursuant to this paper, Applicant submits that elected claims 17-20, 22, 24, 25, 27, 29, 30, 32 and 36 are in condition for further examination and allowance, which action is hereby requested. Upon a finding of allowance for any of the elected claims, Applicant requests rejoinder and allowance of any presently withdrawn claim that is dependent on an allowed elected claim.

If upon considering the amendments and arguments made herein, the Examiner still considers any claim to be unallowable, Applicant respectfully requests that the Examiner provides a detailed explanation as to any remaining deficiencies or reasons for non-allowance.

Date: June 13, 2006

Respectfully submitted,

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